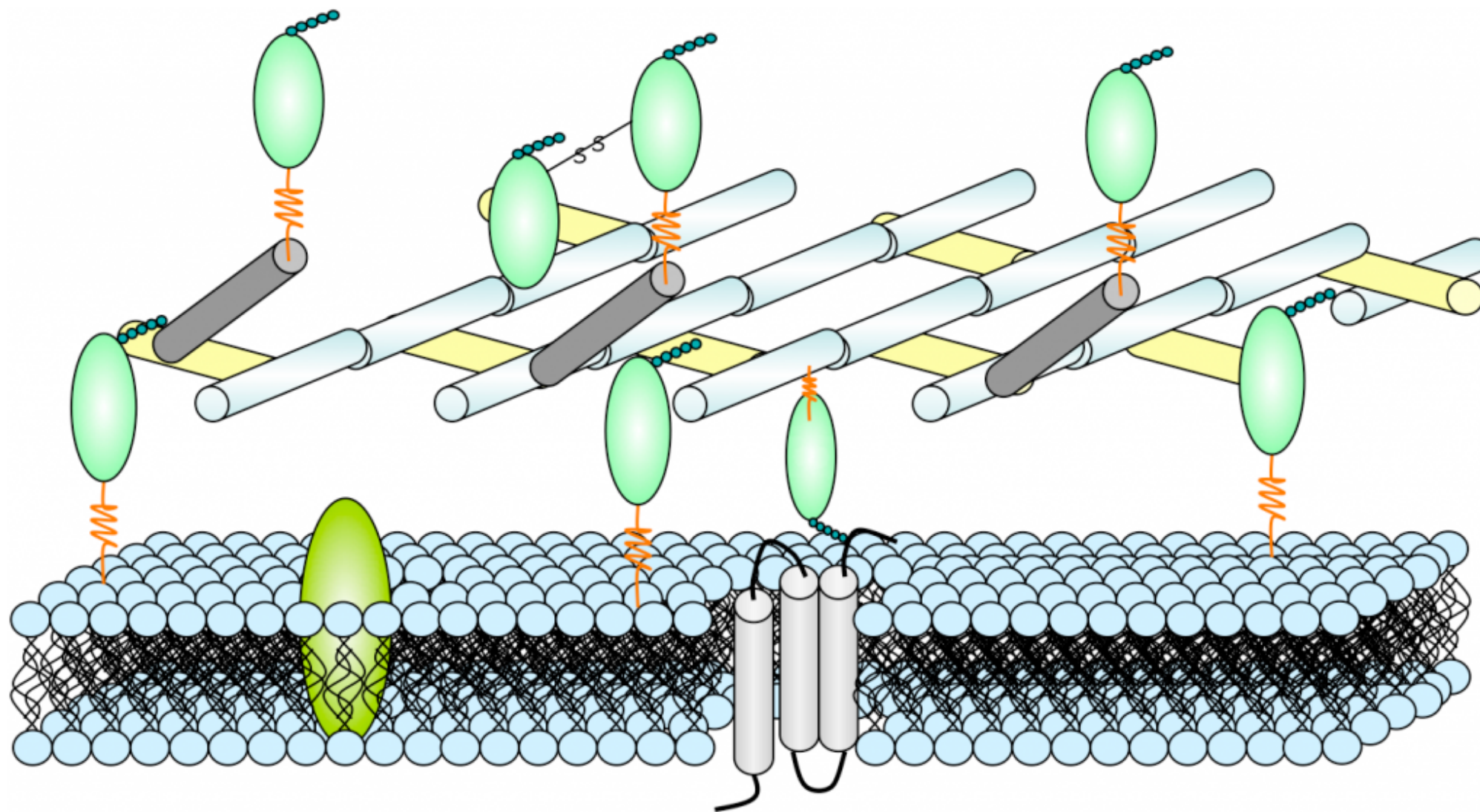


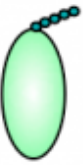
Fungal cell wall

- ▶ Basically consists of β -1,3-glucan, β -1,6-glucan, chitin and mannoproteins, which are interconnected.
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- ▶ Mannoprotein glycosylation and processing occur stepwise throughout the secretory pathway, which is highly conserved from yeast to human

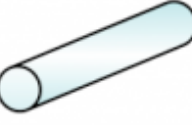
Fungal cell wall

- ▶ β -1,3-glucan and chitin are synthesized by the fungal specific polymerases a number of β -1,3-glucan synthesis inhibitors such as echinocandins, papulacandins and enfumafungin, and chitin synthase inhibitors such as Nikkomycin have been discovered.
- ▶ On the contrary, only a little is known about the synthesis of β -1,6-glucan.
- ▶ The β -1,6-glucan component is a highly branched polymer comprising of about 10% of the total cell wall.

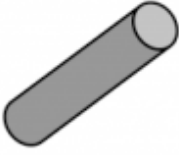



 Mannoprotein
 40%


 GPI Anchor


 β1-3 glucan
 50%

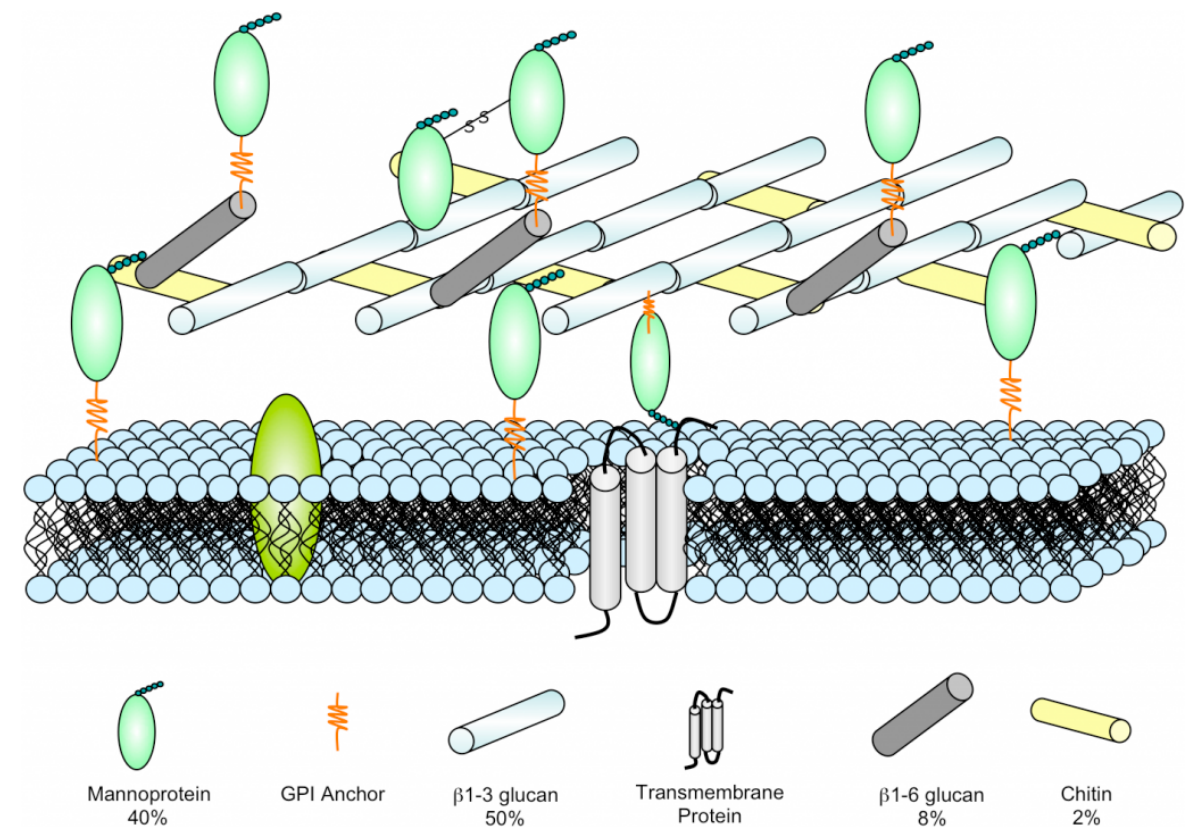

 Transmembrane
 Protein


 β1-6 glucan
 8%


 Chitin
 2%

Fungal cell wall

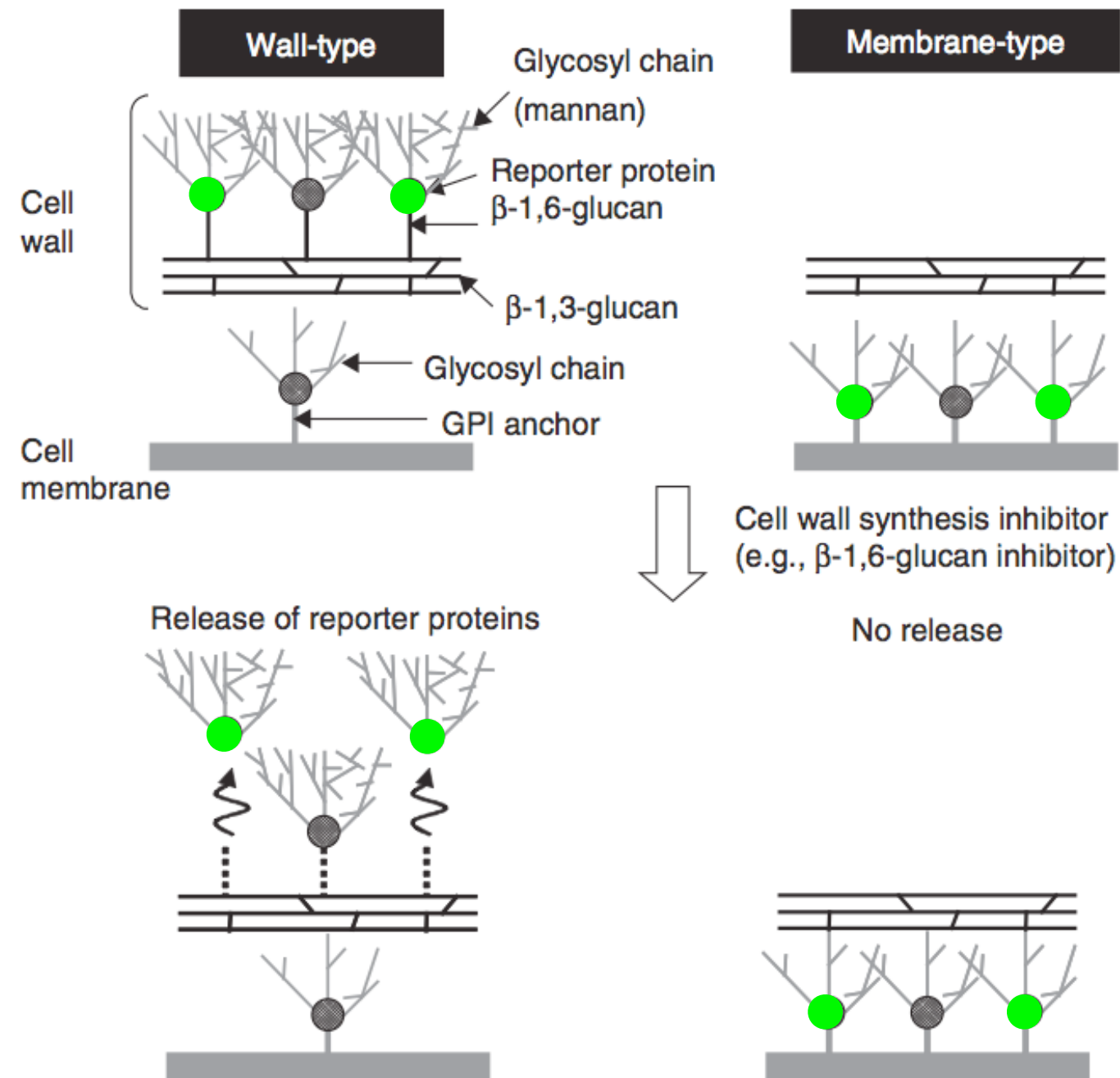
- ▶ > 10 genes identified in the synthesis of β -1,6-glucan.
- ▶ Most have homologues in humans.
- ▶ GPI anchor proteins in *Candida* sp. have specific signals that target them to the membrane or cell wall.



Kitamura et al., 2009. Discovery of a Small-Molecule Inhibitor of β -1,6-Glucan Synthesis. *Antimicrob Agents Chemother.* 53(2): 670–677.

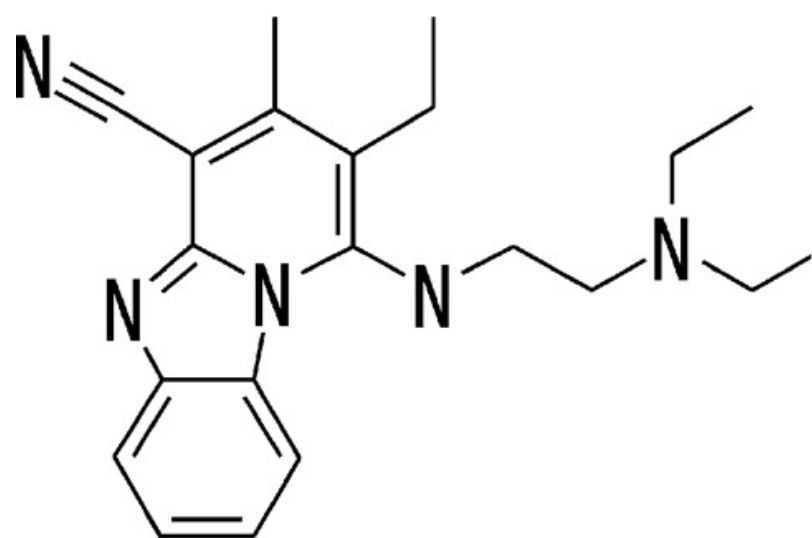
Reporter proteins such as GFP can be targeted to either the cell wall or membrane depending on the targeting signal of the GPI anchor protein

Screen for inhibitors that release the reporter into the medium.

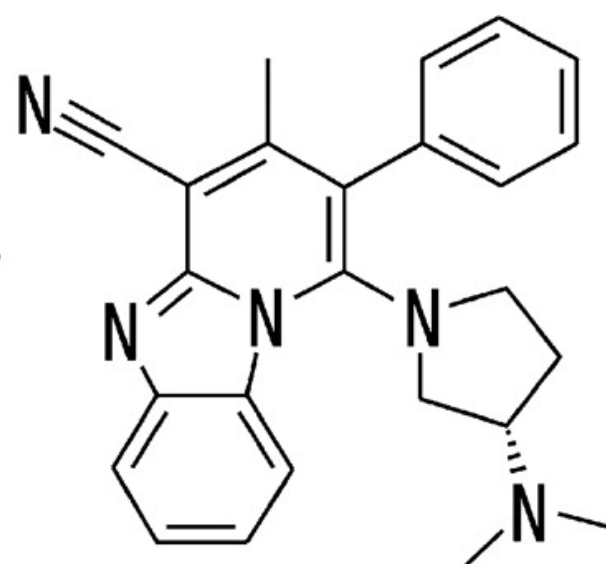


Screening for inhibitors

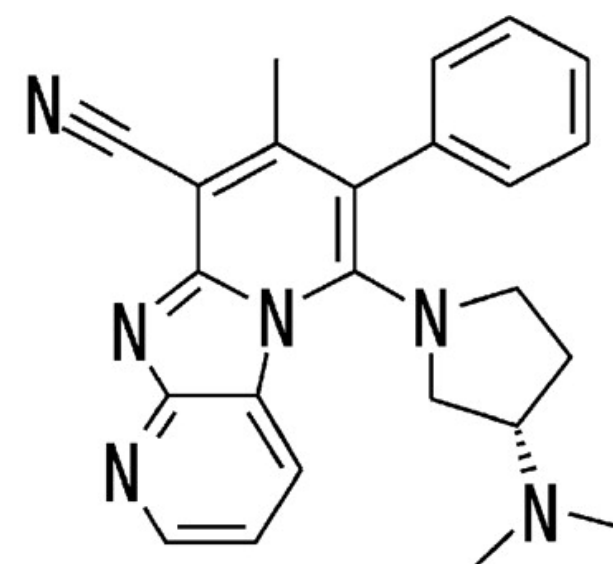
Inhibitors of cell wall synthesis discovered



D75-4590

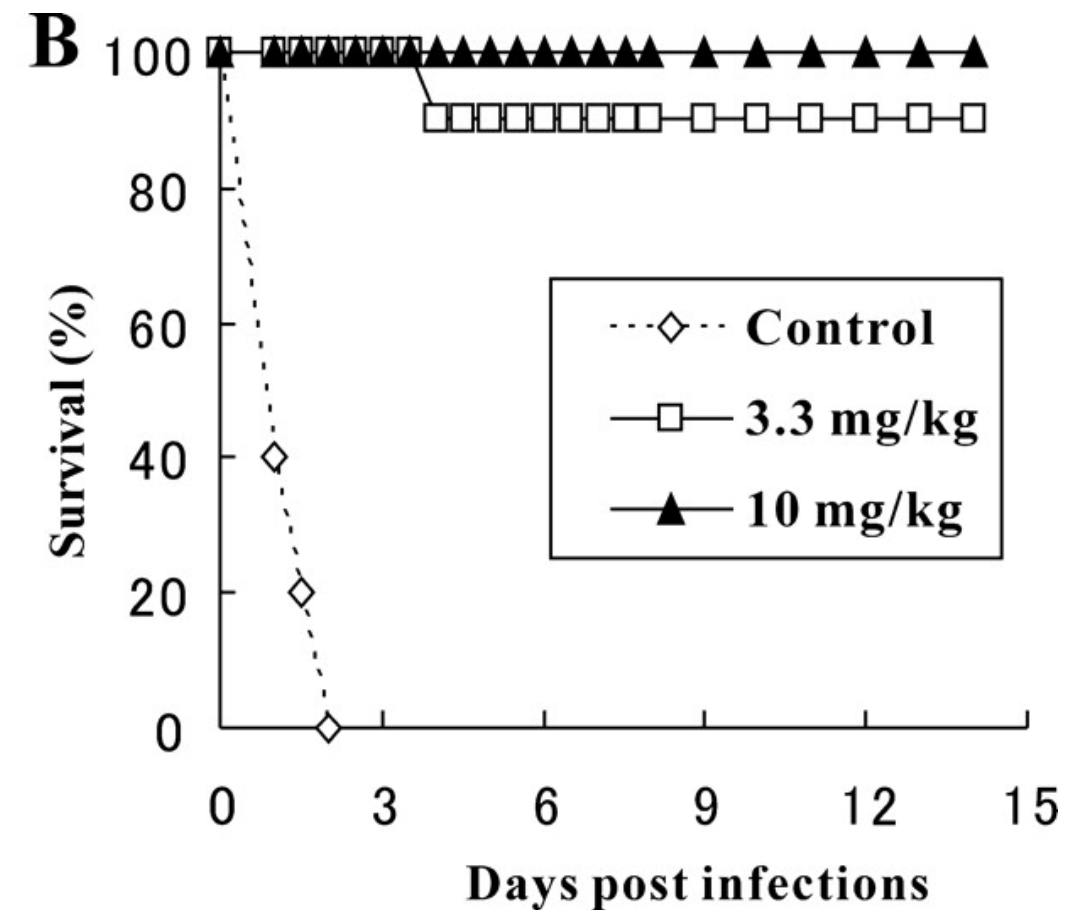
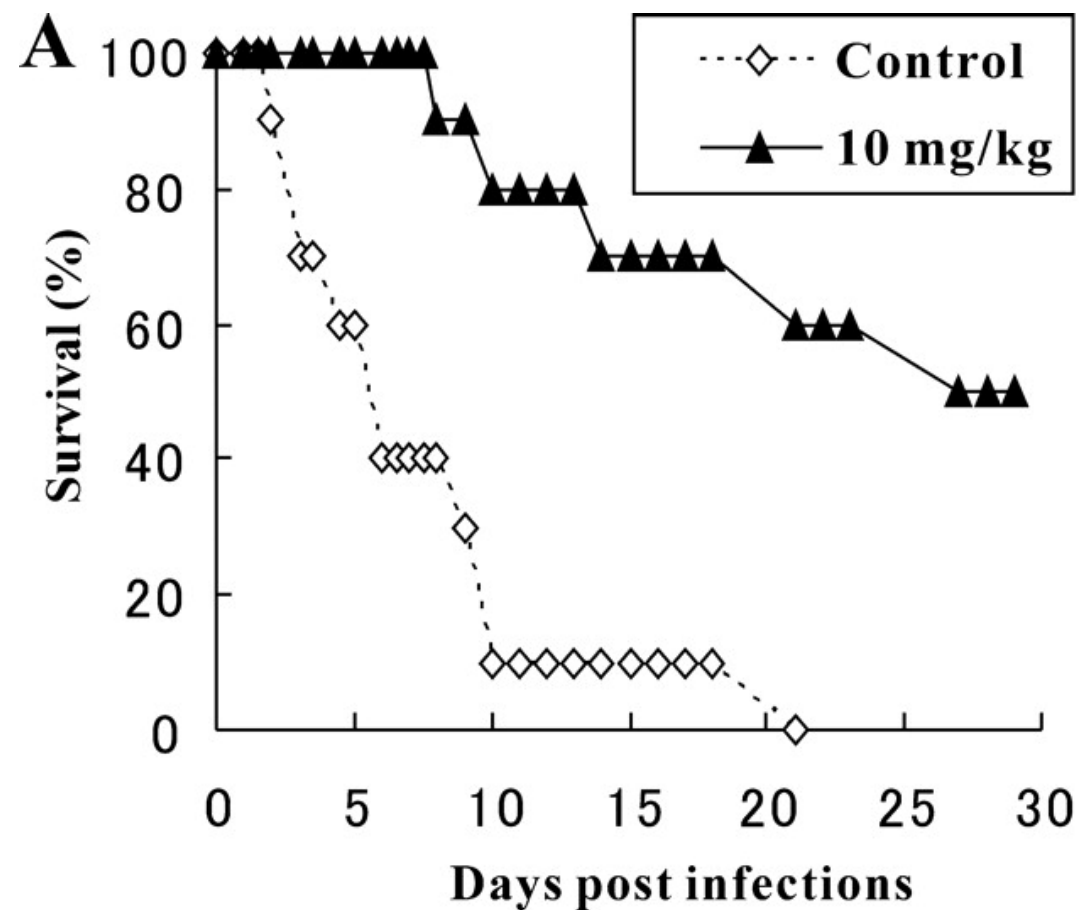


D11-2040



D21-6076

Efficacy of D2I-6076



(A) or *C. glabrata* ATCC 48435 (2.4×10^8 cells) (B). D2I-6076 was administered orally 1, 4, and 7 h after infection.

Summary part 3

- ▶ Knowledge of cell wall biosynthesis can be exploited to develop screens.
- ▶ Proteins unique to fungi are used as the molecular targets
- ▶ Screen is based on disruption of the cell wall biosynthesis.
- ▶ Specific inhibitors discovered.
- ▶ Compounds likely work by preventing the invasion process.